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March 9, 2005

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
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Rockville, Maryland 20852

RE: Docket No. 04P-0544 – Comments in Opposition to Olsson, Frank and Weeda, P.C., Petition for ANDA Suitability of Ondansetron Hydrochloride Injection.

Dear Sir or Madam:

The above-referenced petition should be denied because it proposes a change that is not authorized for approval through an abbreviated new drug application ("ANDA") suitability petition. The proposed change would introduce a single-unit dose of ondansetron hydrochloride injection (8 mg/4 ml in a prefilled syringe, undiluted) that is double that recommended in the approved product labeling. The proposed change is a new dosing regimen, which is not the type of change that may be authorized through an ANDA suitability petition.

Even if we were to assume for the sake of argument that the proposed change is petitionable, introducing this new dose, whether viewed as a new strength or a new dosing regimen, requires significant labeling revisions and raises questions of safety and effectiveness, which require that FDA deny the petition. See 21 C.F.R. § 314.93(e)(1)(i), (iv).

2004P-0544 C1

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Background and Introduction

On December 9, 2004, Olsson, Frank and Weeda, P.C., ("OFW" or "petitioner") filed the above-referenced citizen petition requesting that the Food and Drug Administration ("FDA") permit that an abbreviated new drug application ("ANDA") be filed for ondansetron hydrochloride injection (undiluted) in an 8 mg/4 ml prefilled single-dose syringe (hereinafter the "Citizen Petition").[1] The listed drug, Zofran (ondansetron hydrochloride) Injection, is manufactured by GlaxoSmithKline ("GSK") and is available as follows: 2 mg/ml in a 2 ml single-dose vial (undiluted) and 2 mg/ml in a 20 ml multi-dose vial (also undiluted). GSK also supplies Zofran (ondansetron hydrochloride) Injection Premixed (diluted) as 32 mg/50 ml in 5% dextrose in a single-dose flexible plastic container. According to Zofran labeling, the appropriate dose for prevention of post-operative nausea and vomiting is 4 mg, undiluted, which can be given as a single injection, and the appropriate dose for prevention of chemotherapy-induced nausea and vomiting is 32 mg, diluted in 50 ml of 5% dextrose or normal saline, administered over 15 minutes.

As noted by the petitioner, Abbott Laboratories ("Abbott") previously filed an ANDA suitability petition for the same product that OFW now proposes. Docket No. 04P-0048 (Jan. 30, 2004). This firm submitted comments in opposition to Abbott's request. Docket No. 04P-0048, C1 (March 5, 2004) (copy enclosed). Abbott ultimately withdrew its petition without waiting for FDA's decision.[2]

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1 We note that the Citizen Petition refers to the proposed product as a 4 mg/8 ml prefilled syringe on pages 2 and 7. We assume that these references to the product are typographical errors.

2 Abbott initially requested permission to file ANDAs for multiple ondansetron products. Abbott's earlier petition (03P-0519) requested that the FDA permit that ANDAs be filed for the following: ondansetron hydrochloride injection (4 mg/2 ml and 8 mg/4 ml) in prefilled single-dose syringes and ondansetron hydrochloride injection premixed (8, 12, 16, 20, and 24 mg in 50 ml 5% dextrose injection) in single-dose, flexible plastic containers. Abbott amended that petition by withdrawing its request as to the 4mg/2ml and 8mg/4ml prefilled syringe products and noting that a new citizen petition would be submitted for the 8mg/4ml prefilled syringe. The second Abbott petition (04P-0048) addressed just one out of the seven products originally proposed by Abbott, namely the 8mg/4ml prefilled syringe. Abbott ultimately withdrew both petitions.

For all the reasons set forth herein, as well as those set forth in our opposition to Abbott's request for the same product, FDA should deny OFW's request. The proposed product would provide ondansetron in a single-unit dose that differs from the dosing regimen set forth in the approved product labeling.

Regulatory Framework

Section 505 of the Federal Food, Drug and Cosmetic Act ("FDCA") authorizes the submission of ANDAs, which must include, among other things, information to show that the proposed new drug product has the same route of administration, dosage form, and strength as the already approved listed drug to which the application refers. 21 U.S.C. § 355(j)(2)(A)(iii). An ANDA for a drug product with a different route of administration, dosage form, or strength may be approved only if the change from the listed drug is first authorized through approval of a suitability petition. Id. § 355(j)(2)(C).

FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b).[3] The FDCA and regulations specify the type of changes (route of administration, dosage form, and strength) from the listed drug that are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a). A change in dose or dosing regimen is not the type of change authorized under 21 U.S.C. § 355(j)(2)(C).

Moreover, even where a proposed change is one authorized by statute, FDA must deny an ANDA suitability petition where investigations are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and effective use. 21 C.F.R. § 314.93(e)(1)(i), (iv).

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[3] The substitution of one active ingredient in a combination drug product may also be authorized through a suitability petition. 21 C.F.R. § 314.93(b). That type of change, however, is not at issue here.

Discussion

I. OFW's request should be denied because the product it proposes is a new dosing regimen. Even if the new proposed dose is viewed as only a change in strength, it raises questions of safety and effectiveness and would require significant changes to the approved product labeling.

OFW's request should be denied because it would introduce a new dosing regimen. The change proposed by OFW would introduce a single dose of undiluted ondansetron (i.e., 8 mg/4 ml in a single-dose prefilled syringe), double that of the approved product labeling for prevention of postoperative nausea and vomiting.

There are at least two separate and distinct reasons why OFW's request should be denied. First, a change to the dose or dosing regimen is not the type of change authorized for approval through an ANDA suitability petition. Second, even if we were to assume for the sake of argument that such a change is petitionable, introducing this new dose of the approved product, even if viewed as a new strength, requires significant labeling revisions and raises questions of safety and effectiveness, which require that FDA deny the petition. See id. § 314.93(e)(1)(i), (iv). In addition, absent a waiver, the proposed new product would require pediatric study.

A. OFW has proposed changes that are not authorized for approval through an ANDA suitability petition.

Changes in dose or dosing regimen are not the type of change that can be authorized through an ANDA suitability petition. An ANDA for a drug product with a different route of administration, dosage form, or strength may be approved if the change from the listed drug is first authorized through approval of a suitability petition. 21 U.S.C. § 355(j)(2)(C). FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b). Only these specific types of changes, i.e., route of administration, dosage form, and strength, are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a).

OFW's proposed product is actually a new single-unit dose. Therefore, the petition must be denied as one not authorized under Section 505(j)(2)(C) of the FDCA. FDA routinely denies such ANDA suitability petitions. See, e.g., Letter from Gary J. Buehler, Director, OGD, FDA to Pharmaceutical Associates, Inc. ("PAI") of July 9, 2002.

FDA denied PAI's request to change the strength and volume of drug product administered per dose of hydrocodone bitartrate and acetaminophen oral solution because the change of volume of product per dose changed the dosing regimen. FDA explained that the change in dosing regimen was "not petitionable." Id. OFW attempts to distinguish this precedent, but it is exactly on point because it illustrates that a change in the amount of drug product administered per dose equals a new dosing regimen, which is not a change that may be authorized through a suitability petition. Id.

Apparently in an attempt to fit a category of change that may be authorized through approval of a suitability petition, OFW mistakenly characterizes its proposed product as merely a change in product strength. Based on the approved product labeling, however, there is little need for an 8 mg/4 ml undiluted "new strength" of ondansetron injection. Indeed, the proposed prefilled syringe containing a dose of 8 mg/4 ml of undiluted ondansetron is double that recommended in the approved product labeling for the prevention of postoperative nausea and vomiting.

B. Even if FDA deems OFW's proposed changes petitionable, the petition should be denied because the proposed product would require significant labeling changes.

FDA must deny an ANDA suitability petition where investigations[4] are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and effective use. 21 C.F.R. § 314.93(e)(1)(i), (iv).

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[4] OFW sets forth no medical rationale for the use of its proposed product (i.e., an 8 mg single dose) for the prevention of postoperative nausea and vomiting, nor does it cite any applicable scientific investigations. We note that Abbott in its earlier filed suitability petition for the same product cited a literature review (analysis of published studies) by Tramer, et al., which indicated that "an 8 mg dose may be used intravenously for post operative nausea and vomiting." Abbott Citizen Petition at 3 (2004-P-0048 CP1, Jan. 30, 2004) (emphasis added). As we noted in our opposition to that petition, however, Tramer recognized that the manufacturer, through extensive clinical research, determined that the appropriate intravenous dose is 4 mg. Id. Exhibit III at 39.

The innovator, GSK, provides Zofran (ondansetron) as follows:

1) 4 mg/2 ml single-dose vial (undiluted) (4 mg, undiluted, as a single injection, is the approved adult dose for the prevention of post-operative nausea and vomiting);

2) 40 mg/20 ml multi-dose vial (undiluted); and

3) 32 mg/50 ml in 5% dextrose, premixed in a single-dose flexible plastic container (32 mg diluted in 50 ml of 5% dextrose, given over 15 minutes, is the approved adult dose for prevention of chemotherapy-induced nausea and vomiting; in patients with severe hepatic impairment, a single maximum daily dose of 8 mg infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy is recommended).

If FDA accepts OFW's argument that the proposed product is merely a change of strength, there appears to be little use for the "new strength," based on the current labeling. The only medical rationale that the petitioner offers for the 8mg/4ml undiluted product is that it provides the appropriate dose for patients with severe hepatic impairment, and the correct dose for any individual who happens to weigh 117 pounds (53kg), provided that the drug is being administered in three divided 0.15mg/kg doses.

The currently approved product labeling, however, provides instructions for dose adjustment for hepatic impairment, as well as the option of administering three divided doses, only with respect to prevention of chemotherapy-induced nausea and vomiting. The currently approved product labeling makes no mention of a dose adjustment for hepatic impairment for the prevention of postoperative nausea and vomiting. In addition, the Dosage and Administration section of the approved product labeling indicates that for the prevention of chemotherapy-induced nausea and vomiting the product must be diluted in 50 ml of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration. Undiluted product is appropriate for the prevention of post-operative nausea and vomiting.

Presumably, the only advantage of OFW's proposed product (convenience/efficiency) disappears because in no case will it be ready to use as is. If used to prevent chemotherapy-induced nausea and vomiting, it will have to be diluted. If used for the prevention of post-operative nausea and vomiting, the 8 mg/4 ml prefilled syringe would contain <u>double</u> the recommended dose.

This proposed product, therefore, requires significant labeling revisions to ensure that patients are administered the appropriate dose in the correct form. The draft labeling provided by the petitioner, Citizen Petition Enclosure B, is inadequate. For example, similar to the approved product labeling, page 18 of the draft labeling indicates that ondansetron injection "requires no dilution for administration for postoperative nausea and vomiting." But the draft labeling fails to explain how to divide the 8 mg/4 ml prefilled syringe product into two equal doses. That is, the dosage and administration instructions are unclear with regard to administration to prevent postoperative nausea and vomiting. The draft labeling also fails to indicate whether there are any additional concerns or precautions with regard to storage or stability of a half-used syringe. The proposed product requires significant labeling revisions to ensure that patients receive the appropriate dose.

Moreover, even if appropriately labeled, marketing a single-dose unit that is double that of the reference drug, as OFW proposes, introduces the risk of confusion, which may also lead to patients being administered the wrong dose. FDA is not required to approve a change under FDCA section 505(j)(2)(C) that would heighten the risks associated with the product. See, e.g., Letter from Buehler to Lipomed, Inc of Aug. 1, 2001 (denying ANDA suitability petition where the applicant proposed "doubling of the dose" of cladribine and noting that the agency is not required to approve changes under section 505(j)(2)(C) that involve a heightened risk associated with use of the product).

Indeed, even where FDA has deemed a proposed change to be of a type that is appropriately authorized under Section 505(j)(2)(C) of the FDCA (e.g., a change to either a higher or a lower strength or a change in dosage form), it has routinely denied ANDA suitability petitions that – like the one at issue here – raise questions of safety and effectiveness. See, e.g., Letter from Buehler to The Weinberg Group of Oct. 15, 2004 (denying petitioner's request for a change in amoxicillin and clavulanate potassium dosage form from a powder to a tablet for oral suspension, where clinical trials would be required to address questions of safety and effectiveness and the proposed product could not be used as described in the dosage and administration section of the labeling of the listed drug); Letter from Buehler to Nabeal M. Saif of Oct. 15, 2004 (denying petitioner's request to change the strength from 50 and 100 mg tablets of metoprolol tartrate to 12.5 mg tablets because the proposed product required clinical trials to address questions of safety and effectiveness and was not addressed in the labeling of the listed drug); Letter from Buehler to Shotwell & Carr, Inc. of July 3, 2002 (denying petitioner's request to change strength from 350 mg to 200 mg carisoprodol tablets because FDA had no information to indicate

the lower dose would be effective for the labeled indications); Letter from Buehler to TestoCreme, LLC of April 12, 2002 (denying petitioner's request to change strength from 1% testosterone topical gel to 5% testosterone topical gel).

C. The petition must be denied because the proposed product requires pediatric assessment.

Applications submitted under section 505 of the FDCA "for a new active ingredient, new indication, new dosage form, or new route of administration" are required to include assessments of the safety and effectiveness of the product in the relevant pediatric population. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003), codified at 21 U.S.C. § 355c(a)(1)(A).

By way of background, on October 17, 2002, the U.S. District Court for the District of Columbia invalidated FDA's pediatric rule[5] and enjoined the agency from enforcing it. Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2003). The court did not reach this conclusion based on the merits of the rule, but rather found that the FDA lacked statutory authority to promulgate the pediatric rule. Id.

In 2003, Congress passed The Pediatric Research Equity Act, which codified the pediatric rule. While the statute does not specifically address suitability petitions, the preamble to the pediatric rule did:

> FDA notes that petitions submitted under section 505(j)(2)(C) for a change in active ingredient, dosage form, or route of administration may be denied if "investigations must be conducted to show the safety and effectiveness of" the change. Thus, if a [suitability] petition is submitted for a change that would require pediatric study under this rule, the petition may be denied.

63 Fed. Reg. 66,632, 66,641 (Dec. 2, 1998) (quoting the FDCA).

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[5] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients ("Pediatric Rule"), 21 C.F.R. §§ 201, 312, 314, 601; 63 Fed. Reg. 66,632 (Dec. 2, 1998).

Petitioner asserts that its proposed product is properly viewed as a change in strength, and therefore section 505B of the FDCA is not applicable. As explained above, our view is that the proposed product is a new dose or dosing regimen. We also note that the previous petitioner, Abbott, characterized an 8mg/4ml prefilled syringe as a new dosage form. The requirement to conduct pediatric studies would appear to apply, absent a waiver. The petition includes little scientific justification for failing to study the proposed product in the pediatric population. The petition only states that the proposed product is "likely to be used in patients with severe hepatic failure; such patients are generally geriatric patients." Citizen Petition at 6. The OFW suitability petition does not include a request for a waiver, and therefore the petition should be denied.

II. 180-Day Exclusivity.

The foregoing arguments notwithstanding, in the event that FDA grants OFW's request, the issue remains whether the proposed product would be subject to the 180-day exclusivity, if any, of a generic 2mg/ml ondansetron product. In our comments in opposition to the earlier suitability petition submitted by Abbott for an 8 mg/ 4ml ondansetron prefilled syringe product, we took the position that the product should be subject to the 180-day exclusivity, if any, of a generic version of the 2 mg/ml product. That is, the proposed change to provide the 2mg/ml concentration in a 4 milliliter prefilled syringe is exactly the same as the reference listed drug, i.e., 2 milligrams of ondansetron per milliliter. Doubling the volume of the container does not create a different product.

OFW assumes "for discussion purposes" that our argument is "tenable" with regard to injectable products in multiple use containers, but argues that a single-use dosage form for injection is similar to a single tablet or capsule. Citizen Petition at 7. OFW points out that "FDA regards different container sizes of the same 'strength' of a drug product as the same drug product (e.g., bottles of 100s and 1000s of a 100mg tablet)." Id. OFW argues, however, that a single-use injectable dosage form is more like a single tablet or capsule.

The proposed product at issue here, however, may be viewed as an injectable product in a multiple use container, particularly with regard to its administration for the prevention of postoperative nausea and vomiting. That is, the product proposed by OFW contains two of the recommended doses for prevention of postoperative nausea and

vomiting (4 mg). Therefore, accepting OFW's argument, the product is not a different product for exclusivity purposes and should be subject to the 180-day exclusivity, if any, of a generic version of the 4 mg/2 ml vial product.[6]

Conclusion

For all the aforementioned reasons, the undersigned respectfully requests that FDA deny the OFW suitability petition.

Sincerely,

Robert A. Dormer

Anne Marie Murphy

RAD/AMM/rd

Enclosure

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6 To the extent that FDA's recent listing of different volumes of injectable products in the Orange Book is intended to indicate that they are separate products that can each qualify for 180-day exclusivity, we do not concede that such an interpretation of the statute is lawful.

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3245 '04 MAR -5 P4:14

March 5, 2004

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Rockville, Maryland 20852

RE: Docket No. 04P-0048 – Comments in Opposition to Abbott Laboratories Citizen Petition for ANDA Suitability of Ondansetron Hydrochloride Injection.

Dear Sir or Madam:

The above-referenced petition should be denied because it proposes a change that is not authorized for approval through an abbreviated new drug application ("ANDA") suitability petition. Compared to the current product labeling, the proposed change would introduce a single-unit dose of ondansetron hydrochloride that is double that recommended in the approved product labeling. Although characterized by the petitioner as a "new dosage form," this change is a new dosing regimen, which may not be authorized through an ANDA suitability petition.

Even if the Food and Drug Administration ("FDA") deems the proposed change petitionable, it should deny the petition on one or more grounds. New dosing regimens, like the one proposed, typically require clinical investigation and significant labeling changes, both of which are grounds for denial. In addition, even if FDA accepts the petitioner's characterization of the proposed change, the petition must be denied because

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the safety and effectiveness of any "new dosage form" – including one proposed through an ANDA suitability petition – must be studied in the pediatric population.

Notwithstanding these arguments, if FDA approves the ANDA suitability petition, it should remind the petitioner that the proposed product will be subject to the 180-day exclusivity, if any, of a first filer of a paragraph IV certification for the reference listed drug.

Background

On November 6, 2003, Abbott Laboratories ("Abbott" or "petitioner") filed a citizen petition (03P-0519) requesting that the FDA permit that ANDAs be filed for multiple new single-unit doses of ondansetron. Specifically, that petition proposed the following: ondansetron hydrochloride injection (4 mg/2 ml and 8 mg/4 ml) in prefilled single-dose syringes and ondansetron hydrochloride injection premixed (8, 12, 16, 20, and 24 mg in 50 ml 5% dextrose injection) in single-dose, flexible plastic containers. The listed drug, Zofran (ondansetron hydrochloride) Injection and Injection Premixed, is manufactured by GlaxoSmithKline ("GSK") and is available as follows: 2 mg/ml in a 2 ml single-dose vial; 2 mg/ml in a 20 ml multi-dose vial; and premixed 32 mg/50 ml in 5% dextrose in a single-dose flexible plastic container. According to the Zofran labeling, the appropriate dose for prevention of post-operative nausea and vomiting is 4 mg, undiluted, which can be given as a single injection, and the appropriate dose for prevention of chemotherapy-induced nausea and vomiting is 32 mg, diluted in 50 ml of 5% dextrose or normal saline, administered over 15 minutes.

Recently, Abbott submitted the above-referenced new citizen petition (04P-0048) (hereinafter the "citizen petition"), which requests that FDA permit that an ANDA be filed for just one out of the seven products originally proposed by Abbott, namely the 8mg/4ml prefilled syringe. With the exception of the omission of a few paragraphs that pertained specifically to the products that Abbott dropped from its request, the new citizen petition is

verbatim to the earlier petition. We note, however, that the new citizen petition provides on its face no background or explanation for the change.[1]

On February 4, 2004, this firm submitted to docket 03P-0519 comments in opposition to Abbott's earlier petition. This submission reiterates our objections to the extent that they apply to the 8mg/4ml prefilled syringe proposed by Abbott.

Regulatory Framework

Section 505 of the Food, Drug and Cosmetic Act ("FDC Act") authorizes the submission of ANDAs, which must include, among other things, information to show that the proposed new drug product has the same route of administration, dosage form, and strength as the already approved listed drug to which the application refers. 21 U.S.C. § 355(j)(2)(A)(iii). An ANDA for a drug product with a different route of administration, dosage form, or strength may be approved only if the change from the listed drug is first authorized through approval of a suitability petition. Id. § 355(j)(2)(C).

FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b).[2] The regulations specify the type of changes (route of administration, dosage form, and strength) from the listed drug that are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a).

Moreover, FDA must deny any ANDA suitability petition where investigations are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and

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1 Entered into Docket No. 03P-0519 on February 6, 2004 (the same day that this firm's comments were entered into the docket) is an amendment to Abbott's earlier petition. The amendment withdraws the 4mg/2ml and 8mg/4ml prefilled syringes, provides updated proposed labeling, and notes that a new citizen petition is being submitted for the 8mg/4ml prefilled syringe.

2 The substitution of one active ingredient in a combination drug product may also be authorized through a suitability petition. Id. § 314.93(b). That type of change, however, is not at issue here.

effective use. Id. § 314.93(e)(1)(i), (iv). While a change of drug strength is appropriate for review though a suitability petition, a change in dose or dosing regimen is not because 1) it is not the type of change authorized under Section 505(j)(2)(c) and 2) it would typically require clinical studies and significant labeling changes.

Discussion

I. Abbott's request should be denied because the product it proposes introduces a new dosing regimen, which requires clinical studies and significant changes to product labeling.

Abbott has proposed introducing a single-dose unit containing 8mg/4ml ondansetron injection in a prefilled syringe. The request should be denied because it would introduce a single dose double that recommended in the approved product labeling.

Abbott characterizes its proposed change as an "additional dosage form," but because it is a single-dose unit that contains an amount of ondansetron that differs from what is described in the approved product labeling, Abbott is actually proposing a new dose or dosing regimen. Even if FDA accepts Abbott's characterization of the change as a "new dosage form," the petition should still be denied because applications – including suitability petitions – submitted under FDC Act section 505 that propose, among other things, "a new dosage form" require studies to assess safety and effectiveness in the pediatric population.

The innovator, GSK, provides Zofran (ondansetron) as follows:

1) 4 mg/2 ml single-dose vial (4 mg, undiluted, as a single injection, is the approved adult dose for the prevention of post-operative nausea and vomiting);
2) 40 mg/20 ml multi-dose vial; and
3) 32 mg/50 ml in 5% dextrose, premixed in a single-dose flexible plastic container (32 mg diluted in 50 ml of 5% dextrose, given over 15 minutes, is the approved adult dose for prevention of chemotherapy-induced nausea and vomiting).

Thus, the change proposed by Abbott would introduce a single-unit dose of undiluted ondansetron (i.e., 8 mg/4 ml in a single-dose prefilled syringe) double that described in the labeling.

There are at least two separate and distinct reasons that Abbott's request should be denied. First, a change to the dose or dosing regimen is not the type of change authorized for approval through an ANDA suitability petition. Second, even if we were to assume for the sake of argument that such a change is petitionable, introducing this new higher single-unit dose of the approved product raises questions of safety and effectiveness that require FDA to deny the petition. See 21 C.F.R. § 314.93(e)(1)(i), (iv).

Abbott has proposed a change that is not authorized for approval through an ANDA suitability petition.

Changes in dose or dosing regimen are not the type of change that can be authorized through an ANDA suitability petition. An ANDA for a drug product with a different route of administration, dosage form, or strength may be approved if the change from the listed drug is first authorized through approval of a suitability petition. 21 U.S.C. § 355(j)(2)(C). FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b). Only these specific types of changes, i.e., route of administration, dosage form, and strength, are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a).

Since Abbott's proposed change results in a new single-unit dose, the petition must be denied as one not authorized under Section 505(j)(2)(C) of the FDC Act. FDA routinely denies such ANDA suitability petitions. See, e.g., Letter from Gary Buehler, Director, Office of Generic Drugs, FDA, to Pharmaceutical Associates, Inc. of July 9, 2002 (denying a request to change the strength and volume of drug product administered per dose of hydrocodone bitartrate and acetaminophen oral solution, where the change of volume of product per dose changed the dosing regimen, and noting that the change in dosing regimen was "not petitionable").

The petitioner characterizes the change it proposes as a change in "dosage form" when it is actually proposing a new dose. Indeed, the text of the petition itself is inconsistent on this point. The petitioner demonstrates that it is proposing a new dose for prevention of post-operative nausea and vomiting when it attempts to set forth a medical rationale for the proposed changes: "A review of trials by Tramer et al, indicated that an 8 mg dose may also be used intravenously for post operative nausea and vomiting." Citizen Petition at 3 (emphasis added). If the petitioner were not proposing a new dose, there would be no reason to focus on, or so characterize, this observation by Tramer.

Moreover, Abbott has taken this observation out of context. Tramer, which is a literature review (i.e., analysis of published studies), states the following in its discussion section:

> The lowest intravenous dose tested, 1 mg, was not significantly different from placebo . . . Increasing the dose beyond 8 mg, on the other hand, did not further improve long-term efficacy (at 48 h). The optimal intravenous dose of ondansetron to prevent [post-operative nausea and vomiting "PONV"] is likely to be 8 mg for long-term efficacy, although intravenous doses between 4 mg and 8 mg were not tested in these trials.

Citizen Petition, Exhibit III.

Tramer also recognized that the manufacturer (and FDA) had already determined the appropriate dose and described it in the labeling: "[T]he manufacturer has run an extensive clinical research program to establish the optimal dose and route of administration. The manufacturer concluded that in adults, 4 mg ondansetron was the best intravenous dose for preventing PONV." Id. Exhibit III.

Even if FDA deems Abbott's proposed change petitionable, the request should be denied because the new dose raises questions of safety and effectiveness that would require clinical study and significant labeling changes.

FDA must deny an ANDA suitability petition where investigations are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and effective use. 21 C.F.R. § 314.93(e)(1)(i), (iv). While a change of a drug product's strength is appropriate for review though a suitability petition, a change in dose or dosing regimen, like the ones Abbott proposes, are not because they would require clinical studies and significant labeling changes.

The petitioner's own description of, and cited support for, its "medical rationale" for the proposed changes demonstrates the importance of clinical study of the newly-proposed dosing regimen. Yet, the published studies on which the petitioner relies appear to lack the rigor demanded by FDA to demonstrate the safety and effectiveness of a drug product.

For example, the petitioner indicates that a study by Bernstein and Ong "determined that 8 mg ondansetron IV combined with dexamethasone was effective in controlling

nausea and vomiting in patients receiving moderately and highly emetogenic chemotherapy." Citizen Petition at 3. The study reported by Bernstein and Ong studied only 38 patients, was an open-label design, and lacked any control group. Id. Exhibit IV. Even if FDA were to deem this study adequate, Abbott does nothing to address the concomitant use of dexamethasone in its proposed product labeling.

Even where FDA has deemed a proposed change to be one that is appropriately authorized under Section 505(j)(2)(C) of the FDC Act (e.g., a change to either a higher or a lower strength), it has routinely denied ANDA suitability petitions that – like the one at issue here – raise questions of safety and effectiveness that would require clinical studies and significant labeling changes to ensure safe use. See, e.g., Letter from Gary Buehler, Director, Office of Generic Drugs, FDA, to Shotwell & Carr, Inc. of July 3, 2002 (denying petitioner's request to change strength from 350 mg to 200 mg carisoprodol tablets because FDA had no information to indicate the lower dose would be effective for the labeled indications) and Letter from Gary Buehler to TestoCreme, LLC of April 12, 2002 (denying petitioner's request to change strength from 1% testosterone topical gel to 5% testosterone topical gel).

If FDA accepts petitioner's own characterization of the change it proposes, the petition still must be denied because new dosage form requires pediatric study.

As noted above, the petitioner characterizes the change it proposes as a change in "dosage form." Citizen Petition at 1. Applications submitted under section 505 of the FDC Act "for a new active ingredient, new indication, new dosage form, or new route of administration" require pediatric studies. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, codified at 21 U.S.C. § 355B(a)(4)(A) (emphasis added).

On October 17, 2002, the U.S. District Court for the District of Columbia invalidated FDA's pediatric rule[3] and enjoined the agency from enforcing it. Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2002). The court did not reach this conclusion based on the merits of the rule, but rather found that the FDA lacked statutory authority to promulgate the pediatric rule. Id.

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[3] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients ("Pediatric Rule"), 21 C.F.R. §§ 201, 312, 314, 601; 63 Fed. Reg. 66,632 (Dec. 2, 1998).

Late last year Congress passed, and the President signed into law, The Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003). The new law amends the FDC Act by adding section 505B, Research into Pediatric Uses for Drugs and Biological Products. Section 505B basically codifies the pediatric rule. While the new law does not specifically address suitability petitions, the preamble to the pediatric rule did:

> FDA notes that petitions submitted under section 505(j)(2)(C) for a change in active ingredient, dosage form, or route of administration may be denied if "investigations must be conducted to show the safety and effectiveness of" the change. Thus, if a [suitability] petition is submitted for a change that would require pediatric study under this rule, the petition may be denied.

63 Fed. Reg. at 66,641 (quoting the FDC Act).

Thus, if FDA accepts petitioner's own characterization of the change it proposes, the agency should deny the suitability petition and require that the applicant assess the safety and effectiveness of the "new dosage form" in pediatric patients.

II. The 8mg/4ml prefilled syringe product will be subject to 180-day exclusivity.

The foregoing discussion notwithstanding, in the event that FDA grants Abbott's request, it should remind Abbott that the product it proposes does not differ from the reference listed drug and will therefore be subject to the 180-day exclusivity, if any, of a generic version of the 2 mg/ml product. The proposed product will contain 4 milliliters of ondansetron hydrochloride in the already approved strength, i.e., 2mg/ml.

Abbott's proposed prefilled syringe product is the same strength as the reference listed drug. Abbott's proposed change to provide the 2 mg/ml strength in a 4 milliliter prefilled syringe is exactly the same drug as the reference listed drug, i.e., 2 milligrams of ondansetron per milliliter. Both the proposed product and the reference listed drug contain 2 milligrams of ondansetron per milliliter and both are single-unit dosage forms. Doubling the volume of the container (8 mg/4 ml syringe) does not create a different product. That is, the reference drug, a product containing 4 milligrams of ondansetron in a 2 milliliter container, and Abbott's proposed product containing 8 milligrams of ondansetron in a 4 milliliter container are the same. The only difference is the size of the container.

FDA apparently has an informal policy of requiring suitability petitions for parenteral drug products where the only change from the reference listed drug is the size of the container, not the strength of the drug. Although we are not challenging the wisdom or legality of such a policy at this time, we likewise do not concede that FDA's policy is consistent with the statute. Nevertheless, it is important to acknowledge that a product like the one at issue here – the 8 mg/4 ml prefilled syringe – is the same as the reference listed drug, particularly with regard to its strength.

The strength of a parenteral drug is the amount of active ingredient in a specified weight or volume of the drug, expressed as a concentration or as a percentage. Thus, the strength of the 4 mg/2 ml vial (listed drug) and the 8 mg/4 ml prefilled syringe is the same: 2 mg/ml. These are not different drugs, they are the same drug in a different size (volume) container. This distinction is important because applicability of certain provisions of FDC Act section 505 depend upon whether an ANDA relates to a distinct drug product. And one of the attributes of a distinct drug product is its strength.

The Waxman-Hatch 180-day generic drug exclusivity provision of FDC Act section 505 is affected by how FDA defines "strength." That provision provides exclusivity to a "previous application" for "a drug" when that application contains a paragraph IV certification with respect to listed patents. 21 U.S.C. § 355(j)(5)(B)(iv). The FDA's position with regard to different strength products is as follows:

> The agency has determined that each strength of a drug product can be independently eligible for exclusivity. Applicants may be eligible for a separate exclusivity period for each particular strength of the drug product in an ANDA when each strength refers to a different listed drug . . .. The agency, therefore, has determined that each strength of a drug product is itself a listed drug.

180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications; Proposed Rule, 64 Fed. Reg. 42,873, 42,881-82 (Aug. 6, 1999).

We assume that this is a correct interpretation of the statute. As such, it is important to recognize that the same strength drug packaged in a different size container (e.g. Abbott's proposed 8 mg/4 ml prefilled syringe) is not a distinct drug product as compared to the reference listed drug. Although it may be within FDA's discretion to require that a suitability petition be filed for such a product, there should be no impact on 180-day exclusivity. It is our understanding that FDA has adopted and adhered in previous matters

to the interpretation we propose. That is, FDA has in the past recognized that the 180-day exclusivity granted to a first filer of a paragraph IV certification for the reference listed drug blocks a subsequent ANDA where a change to a different fill volume (but not a change to the drug's strength) was authorized under section 505(j)(2)(C). This policy is consistent with the manner in which the products are listed in the Orange Book.[4] Each injectable ondansetron product is listed by concentration, not fill volume.

Conclusion

For all the aforementioned reasons, the undersigned respectfully requests that FDA deny the Abbott suitability petition. In the event that FDA approves the suitability petition, we request that Abbott be advised that the proposed 8mg/4ml prefilled syringe product is subject to the 180-day exclusivity, if any, of a first filer of a paragraph IV certification for the reference listed drug.

Sincerely,

Robert A. Dormer

Anne Marie Murphy

RAD/vam

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[4] Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") (23rd Edition 2003).